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Understanding Iron Deficiency and Exercise: Looking Beyond Ferritin

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Title: Prevalence of iron deficiency and iron deficiency anemia in strenuously training male army recruits.

## **Editorial Comment**

### **Understanding Iron Deficiency and Exercise: Looking Beyond Ferritin.**

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Iron plays a crucial role in multiple physiological functions and is essential for human health and physical performance, particularly for athletes or military personnel, whose iron requirements may be higher due to factors including increased erythropoietic drive, footstrike hemolysis, menses, gastro-intestinal bleeding, exercise-induced inflammation, anti-inflammatory drug use and environmental stress. Investigations into the effects of strenuous physical activity on iron status have predominantly concentrated on females but in this *Acta Haematologica* issue, Epstein *et al.* describe the development of iron deficiency (ID) and iron deficiency anemia (IDA) in male soldiers. Prevalence of ID and IDA in recruited males was unexpectedly high and increased significantly following the first six months of training, attributed to the continuous physical training[1]. Whilst there is broad awareness of the of ID in females, the evidence reported by Epstein *et al.* show males undertaking arduous military training are also vulnerable to ID and attention should be paid to hematological monitoring and nutritional status of male soldiers and athletes to ensure the detrimental effects of iron deficiency are recognized and treated appropriately.

Prevalence data of ID and IDA is influenced by the diagnostic criteria applied. Epstein *et al.* use cut-off values <14 g/dl for hemoglobin concentration ([Hb]) and <30 µg.L<sup>-1</sup> for serum

ferritin (sFer) to define ID and IDA and they acknowledge that this definition is in contrast to much of the literature. Correctly diagnosing and treating iron deficiency in athletes is a challenge due to: 1. The absence of a clear definition; 2. The absence of a clear treatment and monitoring protocol, particularly if the iron deficiency is not accompanied by anemia (iron deficiency non anemia; IDNA); 3. Training induced plasma volume expansion. Furthermore, sFer is the most commonly used indicator of iron status but sFer criteria vary throughout the literature, ranging from 12-40  $\mu\text{g.L}^{-1}$  [2], whereas in clinical investigations of inflammatory diseases a sFer  $<100 \mu\text{g.L}^{-1}$  might be viewed as ID. The acute phase response of sFer adds further complication, as exercise or illness can cause variation in sFer levels, potentially masking the true value.

Epstein *et al.* and Kell & Pretorius (2014) question the use of sFer for monitoring the iron status of individuals who undergo physical training. Traditionally, sFer is used as an indicator of whole body iron status based on tissue ferritin correlating strongly with iron stores, however, sFer lacks most of the iron it contained in its intracellular form. A more contemporary understanding of sFer is as a marker of inflammation and cell death[3]. Alternative markers are needed. Epstein *et al.* suggest that transferrin saturation (TSat) and transferrin receptor (sTfR) are useful additions to sFer. Although Tsat can be influenced by inflammation, sTfR is not an acute phase protein. Total hemoglobin mass (tHb-Mass) measured by carbon monoxide rebreathing has also been used to assess the effectiveness of iron treatments[4]. Complete blood cell count (CBC) indices assessed alongside [Hb], sFer and Tsat, inform the impact that ID and IDA may be having on reticulocyte and erythrocyte populations. These measurements remain stable in healthy individuals but marked alterations occur in chronic disease states [5]. However, unlike IDA, CBC indices remain unchanged in IDNA, leaving the understanding of this condition largely incomplete. Hepcidin, a peptide hormone that regulates iron absorption shows promise as a key marker of iron status and the influence of strenuous physical activity on hepcidin should be a target of future research. The regulation of hepcidin is mediated by multiple stimuli, including iron

status, inflammation and hypoxia, which are relevant to soldiers and athletes. Longitudinal measurements of acute and chronic exercise exposure together with these biomarker variables would further our understanding of how physical training may affect iron absorption.

Currently, ID can only be confirmed by a positive response to treatment, in the form of an increase in tHb-Mass, however, this retrospective approach still does not allow practitioners to be proactive in the identification and treatment of conditions related to ID. Given that the utility of traditional methods of assessing ID, particularly IDNA, do not provide a definitive insight into the condition it is perhaps time to seek an alternative. Recently, a model has been developed which characterizes the birth rate, maturation and clearance dynamics of red cell populations using raw data from automated hemoanalysers that report single reticulocyte and erythrocyte volume and hemoglobin measurements[6]. Using clinical patient groups Higgins and Mahadevan (2010) have identified patients with anemia and distinguished thalassemia-trait anemia from IDA. The model has also identified pre-anemic states several weeks before anemia has become clinically detectable. This research is based on clinical populations but the findings could have important implications in athletic settings. Early identification of iron deficient states would be significant in the support of the health, wellbeing and performance of military personnel and athletes. It is time for iron deficiency research to look beyond ferritin.

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